TUBERCULOSIS GUIDE

FOR
HIGH PREVALENCE COUNTRIES

MISEREOR

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TUBERCULOSIS GUIDE

FOR HIGH PREVALENCE COUNTRIES

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PREFACE

While tuberculosis has been decreasing so considerably in developed countries during this century, the disease still poses a serious problem in many developing countries, afflicting health and social welfare of millions. Fighting tuberculosis is of major importance to all who are concerned about the health and development of people. Thanks to modern antituberculosis drugs, it has become possible to cure practically all patients suffering from this potentially fatal disease. Successful treatment, however, presupposes combined medication, consistent control and supervision. Our project partners involved in health work conducted by the Church have repeatedly expressed their need for a concise description of how to recognize and combat tuberculosis today in high prevalence countries.

Therefore we are offering them in the following Guide a description of the fight against tuberculosis which was prepared in cooperation with Dr. Annik Rouillon, Executive Director, and Dr. Karel Styblo, Director of Scientific Activities of the International Union Against Tuberculosis.

We hope it will be a useful guide to those who are valiantly shouldering a seemingly overwhelming task in remote rural areas and in overcrowded urban slums. It might also be of interest to health planners and coordinators as well as to those in charge of training the medical profession.

It is understood that any involvement in antituberculosis work requires coordination and cooperation with government health authorities. May this booklet further the fruitful collaboration between governmental and non-governmental health workers, the importance of which was emphasized at the World Health Assembly of May 1985 in Geneva. May it above all be a help towards the successful treatment of those who suffer from a disease which nowadays can be healed.

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PURPOSE OF THE TUBERCULOSIS GUIDE

In many countries the Church and other private agencies take part in the fight against tuberculosis. They often work under difficult conditions in remote areas with only limited medical services available. They feel a growing need for an up-to-date description of the basic principles of diagnosis and treatment of tuberculosis.

This document which has been composed in cooperation with members of the International Union Against Tuberculosis (IUAT) is meant as a guideline for physicians, senior nurses and paramedical personnel involved in the implementation of tuberculosis programmes.

Since the fight against tuberculosis as a public health problem falls under the direct responsibility of government health authorities, all private antituberculosis activities require coordination with the respective governmental offices. In consequence, procedures may have to be modified in concordance with the particular national directives which depend on local circumstances.

This Guide

- **after defining the epidemiological problem posed by tuberculosis and the aim of the fight against tuberculosis (Introduction),**
- **describes the basic principles and procedures of diagnosis, vaccination and chemotherapy (Chapters 2-7),**
- **and concludes by practical advice for recording, reporting and evaluating the various activities involved (Chapters 8-9).**

In addition, the *Appendices* – referred to in the main text – supply information on various technical details. They include a selection of forms useful for laboratory procedures and record keeping (Appendix D) and they comprise the well-known IUAT publication "Technical Guide for Sputum Examination for Tuberculosis by Direct Microscopy" (Addendum).

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INTRODUCTION

The aim of the fight against tuberculosis is

- *for an individual patient:* to cure his disease, to preserve or quickly attain work-capacity, to remain within his family, his ethnic group and the community, and in this way to maintain his socio-economic position;
- *for a community:* to decrease the risk of tuberculous infection in the community and to improve thereupon the tuberculosis epidemiological situation, and in this way to improve the economic and social conditions of the community.

The first *priority* is the *treatment* of tuberculous patients and their cure, especially of patients whose sputum is positive on direct microscopy examination. Smear-positive patients are the most dangerous sources of infection and, without chemotherapy, the outcome of their disease is poor, as two-thirds of them will die within 1-2 years. However, it must be stressed that smear-negative patients must also be given chemotherapy if the presence of active tuberculosis is suspected (for instance, in children, young adult contacts, patients with extra-pulmonary tuberculosis, etc.).

A high priority must also be given to *BCG vaccination* of the newborn and young children.

Chemotherapy and case-finding of tuberculous patients and BCG vaccination of children are in accordance with the Christian, humanitarian and ethical attitudes of physicians, nurses and other members of health services.

In developing countries the fight against tuberculosis can only be successfully conducted within the setting of a National Tuberculosis Programme (NTP). Such a programme must be an integrated part of the general health service of the given country. Rationale, aim and structure of a National Tuberculosis Programme (NTP) are described in Appendix A.

Control measures applied by voluntary and other foreign agencies must fit into the NTP and can only be initiated after a full agreement with the national, regional or district health authorities responsible for the NTP in the respective area.

Close cooperation with the governmental authorities and physicians-in-charge at all levels, as well as with community representatives, is essential for a successful fight against tuberculosis. In addition, village committees and Community Health Workers (CHWs), the church, political parties, etc., should participate in tuberculosis control. It is important to make clear to the population the nature of tuberculosis and its possibility of prevention and cure. It must be stressed to them that the disease is nearly 100 % curable, so that there is no reason for any panic within the community; tuberculosis must not be connected with a stigma as it was in the past. Community participation may contribute to the prevention of tuberculosis – by BCG vaccination ; to case-finding – by encouraging people to seek medical advice if they develop symptoms referable to tuberculosis; and to treatment – by encouraging the patient's compliance.

In developing countries case-finding and treatment can be carried out at the general health facilities and be performed by paramedical workers if they are properly trained and regularly supervised. Case-finding of infectious cases of tuberculosis and their cure are the key to effective control of the disease. Both case-finding and treatment reduce suffering and, if adequately applied, prevent death from tuberculosis.

The annual risk of tuberculous infection in many African countries is about 1.5-3% (corresponding to an incidence of about 75-150 smear-positive cases per 100,000 general population); in South-East Asia, the annual risk is about 2% (corresponding to an incidence of about 100 smear-positive cases per 100,000 population). Some general information on the extent of the tuberculosis problem and its trend in developing countries is given in Appendix B.

1. WHAT IS TUBERCULOSIS?

1.1 Cause of the disease

Tuberculosis is an infectious disease caused, as a rule, by *Mycobacterium tuberculosis.*

Mycobacterium africanum, a variant of *M. tuberculosis,* causes tuberculosis in West Africa. It is known that patients harbouring *M. africanum* show relatively often primary resistance to thiacetazone.

Nowadays, infection caused by *M. bovis* is relatively rare in man. The disease can occur in cows, camels, dromedaries. In most developed countries tuberculosis in cattle was eradicated several decades ago. In developing countries raw milk is not readily available to the population and if it is, milk is usually boiled before consumption.

Infections with mycobacteria other than *M. tuberculosis* or *M. bovis* (i.e. Group I to IV in the Runyon classification) are frequent in developing countries but disease due to them is infrequent (the rare occurrence of the disease is fortunate since these bacilli are nearly always resistant to the majority of antituberculosis drugs).

1.2 Route of infection - Forms of tuberculosis

Infection occurs nearly exclusively through the respiratory system by inhalation of tubercle bacilli. Tuberculosis spreads from the primary lung lesion to other parts of the body by various means: bacilli can be spread by the haematic, lymphatic and bronchial systems or by contact, and in this way can affect other organs.

- *Pulmonary tuberculosis:* Tuberculosis attacks the lungs in more than 80 % of cases. Pulmonary tuberculosis in adults is often *sputum smear-positive* and therefore highly *infectious.*

Cases with sputum positive on culture only or which are culture-negative are approximately 10 times less infectious than those which are positive on microscopic examination of sputum smears. The outcome of such cases, when not treated, is more favourable than that of smear-positive cases.

- *Extra-pulmonary tuberculosis* affects various organs, such as lymph nodes, bones and joints, the uro-genital tract, the nervous system (meningitis), intestines, etc. Diagnosis is often difficult and should usually be made by the doctor. Patients with extra-pulmonary tuberculosis hardly ever spread the disease.
- *Tuberculosis in children:* Sputum cannot often be obtained from children and, in any case, it is often negative even on culture. Diagnosis of tuberculosis rests largely on the results of clinical history, (family) contact history, X-ray examination

and of tuberculin testing. The decision whether or not to treat the child should be made by a Medical Officer.

Generally, any tuberculin-positive child under 5 years who has not been vaccinated with BCG should be regarded as having active tuberculosis and needing a full course of treatment with the standard drugs.

1.3 When should tuberculosis be suspected?

The most common symptoms of pulmonary tuberculosis are:

a) persistent cough for 3 weeks or more, mostly with sputum, sometimes bloodstained;

b) chest pain;

c) loss of appetite and weight, night sweat, fever and shortness of breath.

Tuberculosis is much more probable in patients showing these symptoms who are, or were, also in contact with a tuberculosis case than in those with no known contact.

For extra-pulmonary tuberculosis symptoms depend on the organs involved, e.g.

- swelling of lymph nodes (when these are affected);
- pain and swelling of joints (when joints are involved);
- signs of meningitis when there is tuberculosis meningitis (headache, fever, stiffness of the neck and mental confusion).

1.4 Transmission of infection

Tuberculosis is most commonly transmitted from a person suffering from infectious pulmonary tuberculosis to other persons by infected droplet nuclei. These droplet nuclei are created when the tuberculous person coughs or sneezes. Tiny droplets dry rapidly and the very smallest of them may then remain suspended in the air for several hours. Only those particles of less than 10 micromillimetres in diameter can reach the alveoli, whereas the larger ones will settle in the upper respiratory tract and are removed by the mucociliary stream and usually swallowed.

Other means of transmission of tubercle bacilli, such as handling of contaminated objects, by artificially introducing tubercle bacilli into or below the skin, etc., are very rare and of no epidemiological importance.

Actually, a comparatively small proportion of contacts develop the disease. Firstly, if the tubercle bacillus exists in man's environment, it may not reach the individual man. Secondly, even if it reaches man, it may not multiply and infect him, for a variety of reasons: the number of viable organisms received may be too few to cause infection, also they may not reach the respiratory system with a potentially infective dose, etc. Finally, even if the bacillus succeeds in infecting man, the infection does not frequently result in active disease. This may depend, to an extent, on genetic influences, nutritional state, possible intercurrent infection, etc.

1.5 Health education

Health education should stress the importance of early attendance at a health unit if chest symptoms, especially cough, persist for more than 3 weeks. Patients with these symptoms should ask for a sputum examination at the health centre, dispensary or hospital out-patient department.

1.6 A "case" of tuberculosis

Tuberculosis control, like that of any communicable disease, aims at preventing the spread of infection. The main objective of case-finding in tuberculosis control is to identify sources of infection in a community, i.e. persons who spread infection with tubercle bacilli. In tuberculosis control, a "case" is therefore *any individual discharging tubercle bacilli,* especially if the bacilli in the sputum can be seen by direct microscopy (smear-positive patients).

Bacteriologically unconfirmed cases (for instance in children in contact with smear-positive index cases, in persons with suspected tuberculosis based on clinical and X-ray appearances, persons suffering from extra-pulmonary tuberculosis, etc.) are also treated, as already mentioned, but they must be notified *separately* from those bacteriologically confirmed.

2. DIAGNOSIS OF TUBERCULOSIS

2.1 Case-finding methods

The following methods offer the best prospects of significant yields of cases:

- the examination of patients with relevant symptoms who present themselves on their own initiative at health facilities;
- the promotion of awareness in the community, the medical profession and all medical staff concerning the respiratory symptoms, notably persistent and productive cough, especially if this has been present for more than three weeks and is complicated by bloodstained sputum, chest pain, lost of weight, fever, night sweat, etc.;
- the examination of the household contacts (especially children and young adults) of all smear-positive tuberculosis patients diagnosed;

  N.B. - any tuberculin-positive contact under 5 years of age not previously vaccinated with BCG should be treated as suffering from active tuberculosis (see under 1.2);
- the bacteriological examination of a patient who, for any reason, has had a radiological examination of the chest showing a lesion with a possible tuberculous etiology, which is likely to be active.

2.2 Diagnosis

2.2.1 *Bacteriological examination of sputum* is, as a rule, the only way in which diagnosis of pulmonary tuberculosis can be confirmed in most developing countries.

Whenever tuberculosis is suspected, at least three specimens of sputum should be collected and examined by microscopy. Whenever possible, they should be obtained within two days:

- *first interview with patient.* A *spot specimen* is collected; this is a specimen obtained on the spot after coughing and clearing the back of the throat, under supervision of a staff member. The patient is then given a sputum container for collection of an early morning specimen (a *collection specimen*) before his second interview, which should be on the next day whenever possible.
- *second interview with patient.* The collection specimen is delivered by the patient to the health staff and a further *spot specimen* is collected.

All specimens will be examined in the nearest microscopy laboratory, as a rule, by the Ziehl-Neelsen method. (See Addendum: Technical Guide for Sputum Examination for Tuberculosis by Direct Microscopy.)

Should the first spot specimen be positive by microscopy and should the patient not return for the second interview, an immediate search must be made for him to

prevent dissemination of infection in the community and deterioration of the patient's condition.

A course of symptomatic treatment or (if indicated) antibiotics suitable for non-tuberculous infection (but *not* streptomycin *nor* rifampicin) may be given, whilst awaiting the laboratory smear reports on the specimens.

Should the patient fail to respond to this treatment and remain ill even though the smear was negative, he should be referred for further clinical investigation. In addition, two further specimens of sputum for bacteriological examination for tubercle bacilli should be taken.

N.B.:

- Treatment for tuberculosis will be started as soon as two positive laboratory reports on smear examination are received, or when the patient is severely ill and the clinical suspicion of tuberculosis remains strong. Treatment will not usually be started in the absence of a positive laboratory report (or on the basis of a single positive report) unless it is prescribed by a Medical Officer or the health worker responsible for tuberculosis control in the district.
- On his visit to each health unit the health worker in charge of tuberculosis control in the district will check the documents of all patients diagnosed as tuberculous since his last visit, including those with either a single or no positive laboratory report.

2.2.2 *X-ray* diagnosis of tuberculosis is unreliable, because other chest diseases can look like tuberculosis on X-ray, and pulmonary tuberculosis may show many forms of radiographic abnormality. It must be stressed that X-ray evidence of clinically active tuberculosis is totally unreliable. Consequently, the diagnosis of tuberculosis must, as a rule, be *confirmed by smear or culture examination.*

However, X-ray examination can undoubtedly be very helpful in *clinical* work when tracing tuberculosis among children, young adult contacts, and also in patients suffering from miliary or extra-pulmonary tuberculosis. Clinical diagnosis of tuberculosis based on X-ray examination (in hospital) should always be made by a competent Medical Officer.

In the fight against tuberculosis in developing countries, X-ray examinations are not important nor necessary from the control point of view. The differential diagnosis on X-ray is difficult and is a matter for experts. Moreover, the costs are disproportionately high in relation to case-finding results. Smear examination remains the best way to diagnose pulmonary tuberculosis in developing countries.

2.2.3 The *tuberculin test* in clinical work has a limited value, specially in high prevalence countries. A "positive" tuberculin test is infrequently followed by disease and a "negative" tuberculin test does not exclude, albeit only in a few instances, active tuberculosis. Moreover, a "positive" tuberculin test may be due to infection with mycobacteria other than *M. tuberculosis* or *M. bovis.*

2.2.4 *Diagnosis of extra-pulmonary tuberculosis* depends on the organs involved, and can only be made by a Medical Officer.

2.2.5 *Diagnosis in children* is made by a Medical Officer on the basis of clinical symptoms, the positive Mantoux test (in non-BCG-vaccinated children) and the X-ray.

2.3 Complications of tuberculosis

a. *Pulmonary tuberculosis*

- coughing up of blood (haemoptysis). In all severe cases, i.e. those coughing up the amount of a (small) cup of blood or more, the patients should be prescribed rest, sedatives and antitussives and be referred to the nearest hospital.
- spontaneous pneumothorax (collapse of the lung through damage caused by tuberculosis). The patient must be referred to a Medical Officer for further management.
- pleural effusion. If the amount of fluid is not too great, the clinical condition will improve after treatment with the standard regimen. If there is too much fluid in the thorax, aspiration may be necessary.
- cardio-pulmonary insufficiency (heart and lung disease resulting in *cor pulmonale*). A Medical Officer should be consulted concerning therapy.
- bronchiectasis, fibrosis of the lungs (these are consequences of extensive tuberculosis disease and only symptomatic therapy is possible).

b. *Extra-pulmonary tuberculosis*

Complications depend on the organs involved. A Medical Officer has to be consulted in individual cases.

3. TUBERCULOSIS LABORATORY SERVICES

3.1 Aims of the bacteriological service

The aims of the bacteriological service are, firstly, the diagnosis of new cases and, secondly, the control of the efficacy of their treatment.

The tuberculosis laboratory service in a developing country consists, under favourable circumstances, of a Reference Laboratory for Tuberculosis and a network of multipurpose laboratories throughout the country which carry out microscopic examination of sputum smears stained by the Ziehl-Neelsen method, as part of their work.

The Reference Laboratory for Tuberculosis (department of the Central Laboratory) should be capable of supervising the network of microscopy centres, providing a culture and sensitivity test service in addition to direct smear examination, all at a high technical level.

A practical description of all procedures related to sputum examination by direct microscopy is given in a "Technical Guide for Sputum Examination for Tuberculosis by Direct Microscopy". (A copy is added to this Guide and if reprints are needed for wider distribution, they can be asked from the International Union Against Tuberculosis, 199, rue des Pyrénées, 75020 Paris, France.)

3.2 Extension to the periphery

Efficient peripheral laboratories can play a crucial role in the success of case-finding programmes based on the detection of smear-positive cases. However, how far direct smear examination should be extended to the periphery is a question of local policies and resources. Microscopy centres for examination of sputum for tubercle bacilli are usually located in hospitals and health centres covering about 50,000 to 70,000 population.

3.3. Culture

Culture of tubercle bacilli is necessary for carrying out sensitivity tests, which are of value for guiding retreatment if first-line chemotherapy has failed, and for epidemiological purposes. It might also be of value as a check on the accuracy of diagnosis through direct microscopy. While direct smear examination has the highest priority, the examination by culture of sputum from symptomatic suspects with a pathology on an X-ray of the chest who are smear-negative may result in more frequent and earlier diagnosis.

3.4 Quality control

Quality control of every form of tuberculosis bacteriology, including direct smears cultures and sensitivity tests, is very important but is essentially the task of the Central Unit of the NTP.

3.5 Supervision

The Medical Officer in charge is responsible for supervision in his area.

4. BCG VACCINATION

4.1 Expanded Programme on Immunization

BCG vaccination is in most developing countries included in the Expanded Programme on Immunization (EPI).

All vaccination activities fall under the responsibility of government health authorities. Under such circumstances, private organizations (non-governmental organizations - NGOs) involved in BCG vaccination programmes can pursue their task only in close cooperation with the respective government health authorities.

4.2 Age of vaccination - Method and doses of BCG vaccine

BCG is given as early as possible in life, preferably at birth. The vaccine is injected intradermally, usually on the left upper arm, at the dose of 0.05 ml for those aged 0-1 year (this is the half-dose), and 0.1 ml for those aged more than 1 year (full-dose). (EPI documentation may be obtained via the national EPI or WHO Office.)

4.3 (Re)vaccination at school entry age

In addition, "indiscriminate" (re)vaccination (i.e. without prior tuberculin testing) should be carried out at school entry age (about 6 years) and irrespective of vaccination at birth.

There are several reasons for introducing (re)vaccination at school entry age as a routine:

- the immunological response of infants is poor and it has never been shown that the reduced dose of BCG given to babies affords lasting protection;
- the risk of tuberculous infection in many developing countries is still high (2-3% or more) and most infections occur at school age and after puberty. Vaccination at the age of 6 years should protect children up to about 20 years of age;
- vaccination at school is feasible and, due to growing school attendance, it will cover the vast majority of children in the near future.

4.4 Protection of BCG in children

It is generally accepted that BCG protects children against tuberculosis. This has also been proven in the Indian Prevention Trial when the follow-up period was extended to 12 1/2 years. In children aged 0-14 years on entry, there was no evidence of protection during the first 5 years of follow-up. However, during the next 7 1/2 years, there was a protection of 48% (for details see Tripathy*).

* Tripathy, S.P. (1983): The Case for BCG, Ann. Nat. Med. Sci (India) Vol. 19, 1:11-21.

5. GENERAL ASPECTS OF CHEMOTHERAPY

The only effective treatment of tuberculosis is adequate chemotherapy:

- an *appropriate combination* of three or more antituberculosis drugs,
- prescribed in *correct dosage*,
- *taken regularly* by the patient,
- for a *sufficient period* of time.

The drug must be given to every patient with confirmed tuberculosis. Drugs should be available, free of charge, to every tuberculosis patient detected.

The treatment should preferably include an *initial intensive phase*, since an initial course of intensive triple-drug chemotherapy has the advantage of being more effective in eliminating drug-sensitive bacilli and in minimizing the influence of initial drug-resistant strains.

5.1 Drug resistance

There are 3 types of resistance of tubercle bacilli to antituberculosis drugs, namely natural, acquired and primary:

- a *naturally* drug-resistant strain is a wild strain resistant to a particular drug without ever having been in contact with it. The probability that drug-resistant bacilli (mutants) are present depends mainly on the total number of tubercle bacilli. In *smear-positive* cases of pulmonary tuberculosis, resistant mutants are *always* present, since there are millions of tubercle bacilli inside an average cavity. Mutants resistant to two drugs are rare;
- *acquired* or *secondary* resistance is due to incorrect chemotherapy: for instance, monotherapy with a potent drug (e.g., isoniazid, streptomycin or rifampicin) in patients with smear-positive tuberculosis, or administration of two potent drugs (e.g., isoniazid and streptomycin) to a patient harbouring tubercle bacilli resistant to one of the two administered drugs;
- if a patient with acquired resistance to one or more antituberculosis drug(s) infects a healthy individual, the tubercle bacilli in the infected person are resistant to the same drug(s) as the source of infection, even though the new patient has never taken the drug(s) in the past. This is called *primary* resistance.

Resistance is commonly due to inadequate chemotherapy.

It is, therefore, absolutely essential that chemotherapy in smear-positive patients starts with 3 drugs or more and continues, after the initial phase of 2 months, with 2 drugs.

Newly discovered sputum-positive cases of pulmonary tuberculosis which have never been treated with antituberculosis drugs are sensitive – in more than 90% of all cases – both to streptomycin and Thiazina (isoniazid and thiacetazone). Only in some 4-5% of such cases are the bacilli resistant to isoniazid, in a further 2-3% to isoniazid and streptomycin, and only rarely to streptomycin or thiacetazone alone.

Sputum-positive patients *who have previously taken antituberculosis drugs for 1 month or more* must be suspected of discharging tubercle bacilli *resistant* to isoniazid and/or streptomycin. Such patients must be sent to the referral hospital where a reserve regimen will be applied.

Before treatment is started, it is essential that the patient should be questioned closely and carefully as to whether or not he has previously taken antituberculosis drugs.

5.2 Regularity of chemotherapy

With few exceptions, the regimens under 6.2 will cure most of the newly diagnosed cases of tuberculosis, provided:

- that they are administered for the required period of 12 months,
- that they are taken regularly,
- that the patient on entry is not in a critical condition, and
- that the bacilli are not resistant to isoniazid and/or streptomycin.

Frequent and careful supervision is required to ensure that the patient actually takes all the drugs prescribed. Respected individuals in the community, e.g. secretaries of mass organizations, teachers, etc., can be a great help to health workers in their tasks of ensuring compliance.

5.3 Duration of chemotherapy

It is only of minor benefit to prolong the standard chemotherapy for more than 12 months, provided the patient has taken the regimen without interruption. Chemotherapy should be stopped or temporarily interrupted only if severe drug intolerance or toxicity occurs.

5.4 Procedures during treatment

Bacteriology is much more informative than radiology in following the progress of chemotherapy. The Erythrocyte Sedimentation Rate (ESR) is unreliable in evaluating the progress or results of treatment.

From patients treated with the 12-month (standard) regimen, sputum should be examined at 5, 8 and 12 months after the start of treatment. For procedures for sputum collection, see Section 2.2.1.

- If sputum is *negative* at months 5, 8 and 12, the patient should be discharged from treatment at the end of the 12th month. If sputum was not examined at least

twice, between months 5 and 12, at least two specimens must be taken after month 12 and examined bacteriologically. If the result is negative, the patient should be discharged from treatment; if his sputum is positive, he will be referred for further treatment.

• If sputum is *positive* at month 5, 8 or 12, two sputum specimens should be collected and sent:

- one of them to the local laboratory, for microscopy to confirm the first result, and
- the other to the Reference Laboratory for Tuberculosis, if available, for culture and sensitivity tests. The patient will be referred to one of the referral hospitals, where a Medical Officer will decide on further treatment.

Treatment with Thiazina (isoniazid and thiacetazone) should be continued while waiting for the laboratory report from the Reference Laboratory for Tuberculosis, the patient being urged to take his tablets regularly and, if possible, under stricter supervision.

Streptomycin or a third drug should *not* be added because of the danger of inducing further drug resistance in case the patient is already resistant to the drug(s) he is taking.

If sensitivity tests can be made, subsequent treatment will depend upon these results (continuation with Thiazina (isoniazid and thiacetazone) if the bacilli are sensitive to isoniazid, or a reserve drug regimen if they are resistant to isoniazid).

If culture and sensitivity tests cannot be carried out, assessment for reserve drug treatment should be considered only if the sputum remains positive after a further 2 to 3 months of treatment, unless the patient is seriously ill.

5.5 Follow-up

Subsequent relapse is rare when patients complete the prescribed course of chemotherapy. It is therefore unnecessary to follow up patients who have completed their treatment and who have been declared cured. However, they should be told to report for re-examination if symptoms recur and the procedure described under 2.2, "Diagnosis of tuberculosis", should then be followed again.

5.6 In-patient versus out-patient treatment

Hospitalization *in itself* has little or no effect on the outcome of treatment: if the patient really takes the drugs, he will do equally well whether he is treated in or out of hospital.

In-patient treatment is indicated (often only for a few weeks) for the severely ill, those with tuberculous complications, e.g. haemoptysis, spontaneous pneumothorax or other serious diseases requiring hospitalization. In a number of developing countries, hospitalization is also recommended to ensure that the initial intensive phase of chemotherapy (2 months) is received without defaulting by patients who cannot attend daily for streptomycin because they live far away from the nearest health unit. It is

emphasized that if health staff think that any smear-positive patient will not manage to receive the full initial intensive phase of chemotherapy during the first 2 months, then such patient should be admitted to hospital, even though the policy states that chemotherapy should be mainly ambulatory. For not so severely ill patients, a 2-month "in-patient" treatment in a hostel near the hospital is also possible.

Tuberculosis sanatoria or tuberculosis hospital wards are no longer required.

5.7 Tuberculosis treatment during pregnancy and breastfeeding *

Active tuberculosis in the mother presents a special problem. Pregnant women with active tuberculosis should start or continue their antituberculosis treatment. If the mother has not been treated during pregnancy, she should begin chemotherapy as soon as diagnosis is made. The infant should be given chemoprophylaxis for a minimum period of 6 months or for as long as the mother remains infectious, and then vaccinated with BCG. A brief separation of mother and infant is advisable if possible, when beginning chemotherapy. Meanwhile, if the mother's condition permits, expressed breast milk should be given to the infant, since infection spreads via direct contact with the mother and not through her milk.

Breastfeeding is all the more important since situations where tuberculosis in the mother is diagnosed only after delivery are most likely to occur in populations where environmental conditions are generally very poor, and health risks to the infant are greatest.

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* See WHO A 39/8 Add. 1 p. 5.

6. DRUGS AND REGIMENS

6.1 Drugs

The most important drugs used in the treatment of tuberculosis are isoniazid (H), rifampicin (R), pyrazinamide (Z), streptomycin (S), ethambutol (E) and thiacetazone (T).

Some drugs are available in combined preparations, e.g. isoniazid and thiacetazone (Thiazina or Diateben), rifampicin and isoniazid, and a combination of isoniazid, rifampicin and pyrazinamide.

The time that drugs may be used safely after the manufacturing date, provided that they have been kept in proper conditions (i.e. protected from high temperature and high humidity), is as follows:

Isoniazid	– 5 years
Thiacetazone	– 5 years
Rifampicin	– 3 years
Streptomycin	– 3 years
Pyrazinamide	– 3 years
Ethambutol	– 5 years

6.2 Standard regimens for newly diagnosed cases of tuberculosis

Two main standard regimens are recommended for use in programme conditions in a number of developing countries:

6.2.1 Isoniazid plus thiacetazone (in a combined tablet) daily for 12 months, supplemented, whenever possible, by streptomycin daily for the first 2 months.

6.2.2. A twice-weekly, fully supervised regimen of streptomycin plus isoniazid, preceded, whenever possible, by an initial intensive daily phase of the two drugs for 2 months. The recommended duration of treatment is also 12 months.

The regimen under 6.2.2 is highly effective because it is fully supervised throughout the whole period of chemotherapy.

N.B. If streptomycin cannot be given because of severe side-effects, substitute it with ethambutol per os daily for 8 weeks.

For details of drug dosage for the regimens under 6.2.1 and 6.2.2, see Appendix E, under I.2.

6.3 Short-course chemotherapy for newly diagnosed cases of tuberculosis

Although the standard regimens for new cases (see 6.2) are theoretically 80-85% effective, the success rate achieved by routine treatment in most developing countries

falls to levels in the order of 50% or less. The main reasons for this low success rate are: many patients are detected too late, so that fatality rate after the start of chemotherapy is 10-15%, primary resistance is high (usually 10%) and many patients abscond from treatment after disappearance of symptoms because treatment lasts at least 12 months.

Low treatment success rates among those diagnosed, often combined with late diagnosis and, even more often, with no diagnosis at all (i.e. cases remain unknown and untreated), explain why the tuberculosis situation has remained unchanged in many developing countries for the last two or three decades.

Reasons for negative response to treatment:

- belated diagnosis, disease at an advanced stage
- primary resistance to isoniazid
- irregularity in treatment
- drop-out from treatment
- other causes of non-compliance such as alcoholism, drug addiction, etc.

Recent experiences show that the most promising approach for improving the success rate of chemotherapy in poor developing countries is to use an 8-month short-course regimen comprising an initial intensive and strictly supervised phase of 4 drugs daily (isoniazid, rifampicin, pyrazinamide and streptomycin) for a period of 2 months, followed by 6 months of isoniazid and thiacetazone daily, self-administered. The total cost of drugs for this very effective short-course regimen is about US Dollars 40 per patient, if rifampicin (combined with isoniazid) and pyrazinamide are bought through the International Union Against Tuberculosis (for poor developing countries only).

What are the minimal requirements for introduction of short-course chemotherapy?

- a political commitment by the Government,
- assured availability of the required resources: drugs, means of transport, personnel, laboratory facilities, reporting and recording system,
- the availability of a well-trained and motivated medical and paramedical managerial and supervisory team,
- adequate supervision of drug taking, especially during the initial intensive phase, and proper monitoring of treatment results, and,
- the organization of reliable evaluation procedures based on a good, but simple information and recording system.

For details, see Appendix E.II.

6.4 Chemotherapy of previously treated patients

Sputum-positive patients who have previously taken antituberculosis drugs for more than 1 month must be suspected of discharging tubercle bacilli resistant to

isoniazid and/or streptomycin. These patients should be considered for retreatment regimens.

Eligible for retreatment are:

6.4.1 *Smear-positive relapses*

These are patients with smear-positive pulmonary tuberculosis, previously treated for active tuberculosis (bacteriologically confirmed or unconfirmed) who were declared "cured" after completion of a course of chemotherapy of tuberculosis.

6.4.2 *Smear-positive failure cases*

These are patients:

- who do not or only temporarily show sputum conversion while receiving the standard or short-course chemotherapy for newly diagnosed cases of tuberculosis, or
- who are positive by direct smear while returning to treatment after having defaulted for more than 3 months after the start of treatment.

Chronic excretors of tubercle bacilli (individuals who have been discharging tubercle bacilli for more than 2 years) are usually resistant to more than two drugs and their treatment is, in general, extremely difficult and expensive. The Medical Officer in charge will decide – in consideration of the humanitarian, ethical and medical aspects involved – whether the patient is eligible for the retreatment regimen.

The retreatment regimen which is recommended consists of an initial intensive phase of daily rifampicin (combined with isoniazid), pyrazinamide and ethambutol for essentially 3 months (12 weeks), supplemented by streptomycin for the first 2 months (8 weeks). The continuation phase depends on the results of sensitivity tests (if available) on sputum taken before the start of retreatment:

- patients harbouring strains which were fully or partially resistant to isoniazid on entry will continue with rifampicin (combined with isoniazid) and ethambutol three times a week under supervision for a period of 5 months;
- patients harbouring strains which were fully sensitive to isoniazid on entry will continue with daily Thiazina, for a total period of 5 months.

N.B. If no culture facilities are available, the patient will continue with rifampicin (combined with isoniazid) and ethambutol three times weekly for a period of 5 months.

For details, see Appendix E.III.

6.5 Contacts of smear-positive index cases

- *Children aged 6 and over and adults:* Any person who coughs and who was in contact with a smear-positive index case should have two sputum examinations, the first as soon as possible after the index case has been diagnosed and the second 3 months later.

– *Children aged 5 years and under:* Any tuberculin-positive contact aged 5 years or under, not previously vaccinated with BCG, should be treated as suffering from active tuberculosis, i.e. Thiazina for 12 months, supplemented by streptomycin for the first 8 weeks.

If the tuberculin test is negative and the child has not been vaccinated previously with BCG, give Thiazina for 3 months and repeat the tuberculin test at the end of the 3-month period. If the test is still negative, give BCG vaccination and stop chemotherapy.

N.B. *Newborns:* If non-BCG-vaccinated, give isoniazid for 3 months. Test for tuberculin sensitivity at the end of the 3-month period. If the test is positive, treat for 6 months in all. If negative, give BCG vaccination. Breast-feeding is safe and should be continued (see 5.7).

7. SIDE EFFECTS OF ANTITUBERCULOSIS DRUGS

Side-effects of antituberculosis drugs should be divided into two groups:

- *Minor side-effects* cause only relatively little discomfort; they often respond to symptomatic or simple treatment but occasionally persist for the duration of exposure to drugs.
- *Major side-effects* are those giving rise to serious health hazards.

7.1 Rifampicin

When given in the recommended dosage, rifampicin does not cause side-effects with great frequency, particularly during continuous daily administration.

One of the major side-effects of rifampicin is hepatitis, although this is rare. Alcoholism, pre-existing liver disease, or the simultaneous administration of other hepatotoxic agents seem to increase the risk. The development of jaundice requires discontinuation of the drug.

Two serious, uncommon side-effects may occur:

- a respiratory syndrome consisting of shortness of breath rarely associated with collapse and shock. Such cases require immediate, adequate hospital care;
- purpura and other rare reactions, such as acute haemolytic anemia, shock and renal failure. If any of these occur, rifampicin must be stopped immediately and never be given again. Immediate hospitalization is mandatory.

Minor reactions observed with regimens containing rifampicin are:

- a cutaneous syndrome consisting of flushing and/or pruritus, with or without rash, involving particularly the face and scalp, often with redness and watering of the eyes;
- a flu syndrome consisting of attacks of fever, chills, malaise, headache and bone pains, the latter being sometimes severe;
- an abdominal syndrome consisting of pain and nausea, sometimes accompanied by vomiting or, less commonly, diarrhoea.

The cutaneous syndrome is often self-limiting and does not usually require more than symptomatic treatment. The flu syndrome, usually mild, requires no change of treatment. The abdominal syndrome requires only symptomatic treatment; try to give rifampicin during or after meals.

Rifampicin may impart an orange-red colour to the urine, faeces, saliva, sputum, tears and sweat. This is without pathological consequences but patients should be warned of it.

7.2 Isoniazid

The side-effects include:

- various skin rashes;
- signs of neurotoxicity (paraesthesia, numbness, and muscle pains in cases of peripheral neuritis) or confusion;
- pellagra-like syndrome.

These side-effects can be minimized by the administration of pyridoxine (Vitamin B6, 10 mg daily, or Vitamin B-complex). Liver disturbances are observed.

7.3 Thiazina

Thiazina in doses of 300 mg isoniazid and 150 mg thiacetazone daily in a single dose in adults is well tolerated in many African countries, but it is less well tolerated, for instance, in South-East Asia.

A minor but relatively common side-effect of Thiazina is decreased haemoglobin level for the duration of treatment, which improves on its completion. Less common minor side-effects are gastrointestinal upsets (nausea, vomiting, diarrhoea). Symptoms usually subside if the daily dose is divided and given half in the morning and half in the evening for a week or so. Sometimes antacids are recommended.

Among major side-effects, hepatitis develops in about 0.5% of cases. If hepatitis is suspected or if jaundice is observed, stop treatment. When hepatitis clears the patient should be transferred to a referral hospital for further tuberculosis treatment.

Very occasionally there are signs of neurotoxicity, namely peripheral neuritis and/or confusion due to isoniazid. Treat with pyridoxine (10 mg daily) or a pyridoxine-containing vitamin B-complex preparation.

Cutaneous reactions in patients treated with Thiazina (these reactions are due to thiacetazone) may be more serious than with other drugs. Exfoliative dermatitis or Stevens-Johnson syndrome may occur. Stevens-Johnson syndrome is a special type of hypersensitivity reaction characterised by a generalised bullous eruption, sometimes haemorrhagic, involving skin and mucous membranes. Thiazina should be stopped immediately and *never* be given again. Immediate cortico-steroid treatment is indicated; therefore the patient must be sent without delay for admission to hospital and emergency treatment.

Agranulocytosis, a very rare complication of Thiazina treatment, is manifested by increasing pallor, sore throat, soreness of mouth, gum infection and a tendency to bleed. The patient must be immediately admitted to hospital for full haematological examination and treatment.

7.4 Streptomycin

Transient and minor side-effects, such as local reaction at injection site, numbness

around the mouth and tingling may occur soon after injection. If the reaction is troublesome – an infrequent occurrence – the dose may be reduced by 0.25 g.

The main toxic effect of streptomycin is vestibular damage. The risk increases with the dose and age. (The dose of 1 g is, therefore, reduced to 0.75 g in persons weighing less than 50 kg and in those aged 45 years or more.) Damage to the vestibular system usually occurs in the first 2 months and is manifested by ringing in the ears, giddiness and ataxia. The condition is reversible if the drug is stopped or the dosage reduced by 0.25 g. (If the drug is stopped continue treatment with Thiazina only.) If treatment continues, the vestibular damage may become worse and permanent (loss of balance and deafness). The risk is particularly high in patients with impaired excretory function of the kidneys.

Hypersensitivity reactions occasionally occur, like a sudden onset of fever often accompanied by headache, vomiting and an irritative erythematous rash. Stop treatment (both streptomycin and Thiazina) and admit the patient to hospital for hypersensitivity testing and desensitisation procedure.

7.5 Ethambutol

Ethambutol may produce impairment of vision – a decrease in visual acuity, blurring and red-green colour blindness. However, ocular toxicity seems to be clearly dose-dependent and occurs only rarely when 20 mg/kg body weight are given daily and 30 mg/kg body weight twice weekly (see p. 51 under N.B. 2).

Every patient receiving ethambutol should be warned that, if visual symptoms occur, an ocular examination should be undertaken. Impaired vision usually returns to normal within a few weeks when the drug is stopped. It is because of the risk of undetected ocular toxicity that ethambutol should not be given to children.

7.6 Pyrazinamide

The main side-effects of pyrazinamide are hepatitis, joint pains and sometimes attacks of gout, probably due to the diminished excretion and accumulation of uric acid.

Occasionally, hypersensitivity reactions, such as fever and rash, and other cutaneous reactions may be seen.

7.7 Prothionamide

Side-effects of prothionamide are uncommon and – when observed – mild (gastrointestinal symptoms, dizziness, headaches, vertigo, paraesthesias).

7.8 Hypersensitivity reactions to drugs

In all severe reactions: stop all drugs and refer the patient to hospital. In hospital the patient will be rested and given steroids in high doses, e.g. prednisolone. When

the reaction has subsided, the drug which was the source of the reaction should be detected. This is done by giving small doses of one drug at a time, increasing gradually to the full dose (according to body weight and age).

Isoniazid, 100 mg tablets

1st day – 25 mg (1/4 tablet)
2nd day – 50 mg (1/2 tablet)
3rd day – 100 mg (1 tablet)
4th day – 200 mg (2 tablets)
5th day – 300 mg (3 tablets)

Careful examination of the patient is essential before giving the next higher dose. If there is a reaction at a given dose (e.g. 4th day with 200 mg), go back to the next lower dose (e.g. 3rd day with 100 mg) and increase the dose daily again.

Once a drug is given in full dose without incident (taking into account body weight and age), administration of that drug should be continued while test doses of the other drugs are given.

Streptomycin

1st day – 125 mg
2nd day – 250 mg
3rd day – 500 mg
4th day – 750 mg
5th day – 1,000 mg

Take the same precautions as for isoniazid.

Thiazina (isoniazid 100 mg, thiacetazone 50 mg)

If there is no reaction to isoniazid and streptomycin, try thiacetazone as follows (in accordance with body weight and age):

1st day – 12.5 mg (1/4 tablet)
2nd day – 25 mg (1/2 tablet)
3rd day – 50 mg (1 tablet)
4th day – 100 mg (2 tablets)
5th day – 150 mg (3 tablets)

When the drug causing the reaction is detected, that drug should not be given again. A patient who reacts to any of the standard regimen drugs should be sent to the referral hospital for desensitisation and management.

8. RECORDING AND REPORTING

The accurate keeping of records on all individual patients, and periodical reporting – with statistics on patients and activities, together with explanatory remarks – is essential for planning of procurement of drugs, laboratory reagents, sputum containers, of hospital beds for tuberculosis, of manpower, etc., as well as for evaluation of control measures applied in the tuberculosis programme.

The number of documents used in the programme has to be limited as much as possible and they should be clear and simple. The following recording and reporting materials should be considered:

- Tuberculosis Laboratory Register: kept at laboratories carrying out sputum examination for tubercle bacilli ;
- Tuberculosis Register: kept at district or health centre level;
- Tuberculosis Treatment Card for each patient under treatment (for recording injections of streptomycin, drug collection, clinical notes, etc.): kept in all health units giving chemotherapy;
- Patient's Identity Card: kept by the patient;
- Request Form for Sputum Examination (treatment unit; new patient/follow-up of chemotherapy; date of sputum collection; results of sputum examination, etc.): kept in all health units;
- Request Form for Culture and Sensitivity Tests of *M. tuberculosis:* kept in hospitals;
- Quarterly Report on Case-Finding: kept at district or health centre level by a health worker responsible for the NTP;
- Quarterly Report on Results of Chemotherapy of Smear-positive Cases of Pulmonary Tuberculosis registered 15-18 months earlier: kept at district or health centre level by a health worker responsible for the NTP.

The results of *chemotherapy* should be reported as follows:

: cured (smear-negative at 5, 8 and 12 months with the standard chemotherapy, and at 5 and 8 months with short-course chemotherapy);

: chemotherapy completed (no smear results);

: died;

: positive after 8 months (short-course chemotherapy) or 12 months (standard chemotherapy);

: lost from sight (defaulter);

: transferred out (to another district).

For specimens of proposed registers, forms and cards, see Appendix D.

9. EVALUATION

A built-in evaluation system is an integral component of any tuberculosis programme. It deals with two distinct subjects:

9.1 Evaluation of control measures applied

It is mandatory to collect regularly information on smear-positive cases detected (newly reported cases must be separated from other smear-positive cases such as relapses, failure cases, chronic tuberculous excretors, etc.) and on the results of chemotherapy.

a. *Evaluation of case-finding*

The most important part of evaluation of the case-finding programme is to compare the expected and the observed rates (per 100,000 population) of *smear-positive* pulmonary tuberculosis cases. The *observed* rates can be calculated from the "Quarterly Report on Case-finding".

The *expected* rates can be estimated from the annual risk of tuberculous infection (see Appendix B).

b. *Evaluation of treatment*

"Quarterly Report on Results of Chemotherapy of Smear-positive Cases of Pulmonary Tuberculosis: a cohort analysis" is the most important part of the evaluation of the programme. The results of treatment are given as follows:

- cured (smear-negative);
- chemotherapy completed (no smear results);
- died;
- positive after 8 months (short-course chemotherapy) or 12 months (standard chemotherapy);
- lost from sight (defaulter);
- transferred out (to another district).

9.2 Evaluation of the impact of control measures on the epidemiological situation of tuberculosis and its trend.

See Appendix B.

GLOSSARY

Age-specific prevalence – age-specific rates – (see incidence, prevalence, or mortality) relate the number of cases or deaths recorded for each age-group to the total number of persons in the corresponding age segment of the population. The age-specific rates are usually defined in 5-year intervals or multiples thereof, for example 0-4 year-olds, 5-9, 10-14, 15-24, 25-34, and so on.

Agranulocytosis – disappearance of neutrophil polymorphonuclears from the peripheral blood. In practice, this term also includes extreme neutropenias, below 300 granulocytes/mm^3. This syndrome involves a severe infectious risk with necrotic angina. When not accompanied by other signs and symptoms, it is most commonly related to an immuno-allergic mechanism, for instance following the intake of drugs such as thiacetazone, etc.

Alveoli (pulmonary alveoli) – microscopic pulmonary structures, more or less octahedral, connected to the alveolar saccules, and forming the distal terminal mode of the intra-pulmonary airways. Alveolar walls are distinguished by the presence of special cells which enable rapid exchange (diffusion) of oxygen and carbon dioxide. It is in the alveolar space thus determined that hematosis occurs (zone of exchange).

Annual average risk of tuberculous infection – the annual average risk of tuberculous infection indicates what proportion of the population will be infected (whether primarily infected or reinfected) with tubercle bacilli in the course of one year. It is usually expressed as a percentage or as a rate. The annual average risk of tuberculous infection is sometimes referred to as the "annual risk of tuberculous infection", "the risk of tuberculous infection" or "the annual tuberculosis infection rate".

Case-finding – is an essential component of the control of tuberculosis. Its object is to identify the sources of infection in a community, e.g. in the case of tuberculosis, to find persons who are discharging tubercle bacilli. By rendering them non-infectious through chemotherapy, the chain of transmission of tubercle bacilli from man to man is cut.

Chronic excretor of tubercle bacilli – a patient who has been excreting tubercle bacilli for more than 2 years.

DMO – District Medical Officer.

Drug intolerance – the occurrence of unpleasant but *not* life-threatening side-effects of a certain drug. Such side-effects may dampen the willingness of a patient to comply with his treatment and may result in default if left unattended by medical staff. (For severe side-effects see "Toxicity".) Examples of drug intolerance: nausea

and gastrointestinal disturbances due to thiacetazone, attacks of gout due to pyrazinamide, flu syndrome due to rifampicin.

EPI – Expanded Programme on Immunization.

Failure case – a patient who was smear-positive at the start of chemotherapy and who does not, or only temporarily, show sputum conversion while receiving chemotherapy. The most frequent reason for failure is that the patient absconded from treatment or took the prescribed drugs irregularly or in low doses. Another reason is that the bacilli are resistant to one or more drugs given to the patient.

First-line chemotherapy – the therapy which has been selected in a certain programme for the treatment of new cases. The term is used in contrast with second-line chemotherapy, i.e. the therapy selected for retreatment of relapse or failure cases.

Haemoptysis – spitting of blood coughed up from the sub-glottic respiratory system (this generally refers to red blood emitted through forced coughing).

Incidence – tuberculous incidence indicates the number of new cases of tuberculosis which develop within a specified period of time, usually one year. It is usually expressed as a rate per 100,000 general population. The incidence should be given separately for:

- patients excreting tubercle bacilli demonstrable by direct smear examination,
- those excreting tubercle bacilli demonstrable by culture only,
- culture-negative cases of pulmonary tuberculosis, and
- extra-pulmonary tuberculosis.

In most cases, the time of onset of the tuberculous disease cannot be determined. The expression "incidence" is therefore usually replaced by the term "newly notified", "newly discovered" or "newly reported" cases of tuberculosis per 100,000 general population.

Index case – see "Smear-positive index case".

Lethality – tuberculosis lethality rate indicates the number of deaths from tuberculosis per 100 cases of the disease. It usually refers to the incidence of tuberculosis (newly reported cases) followed up for say 2, 5 or 10 years.

Monotherapy – treatment with one drug only. Monotherapy in patients with bacillary tuberculosis results, as a rule, in development of resistance against the drug used. Prescribing only one drug for the treatment of tuberculosis of any kind is considered to be a serious art failure.

Adding another drug to a prescribed regimen when a patient is not responding well to that regimen should effectively be considered as monotherapy, since it is likely that resistance to the drug(s) of the original regimen has developed. One should, therefore, never add one drug only to the regimen of a patient who is not responding well.

Monotherapy should be distinguished from *chemoprophylaxis* which is sometimes

given to individuals who have been infected with *M. tuberculosis* but who do not have a manifest disease. Isoniazid is the drug of choice for chemoprophylaxis.

Mortality – tuberculosis mortality rate indicates the number of deaths from tuberculosis in a given population. The death rate is computed per year per 100,000 general population.

Tuberculosis mortality should be distinguished from tuberculosis lethality.

Mucociliary stream: mucus – clear, filaceous, hydrosoluble product, secreted under normal conditions by the mucous glands, which protects epithelial surfaces both from the mechanical and chemical points of view. Mucine is its main constituent. A thin layer of mucus continuously streams from the small airways in the direction of the throat thus keeping the airways clean.

Notification rate: see "Incidence".

NTP – National Tuberculosis Programme.

Prevalence – tuberculosis prevalence gives the number of cases of tuberculosis present in a defined population at a particular date per 100,000 general population ("point prevalence").

Pruritus (itching pruritus) – spontaneous rash sensation located on the skin or mucous membrane, which is a particularly common functional sign. It is common as an allergic reaction to drugs. When there is intense scratching for a long period of time, this can result in secondary lesions: erythema, linear excoriation, lichenification.

PTC – Provincial Tuberculosis Coordinator.

Purpura – extravasation of blood out of the capillaries of skin or mucous membrane which may produce petecchias or an ecchymosis. It rarely occurs as an allergic reaction to drugs.

Quality control – monitoring of the reliability with which a certain test or activity is performed: an important form of quality control in a tuberculosis programme is the monitoring of direct smear microscopy performed at peripheral laboratories, since unreliable results (false-positive or false-negative) may lead to wrong decisions regarding the management of a patient. If a national programme does exist quality control will usually be organized at central level (e.g. by a Tuberculosis Reference Laboratory) but it may be organized locally by a person knowledgeable in direct smear microscopy. A simple method would be for this experienced person to check all smears with a positive reading at the local laboratory and a sample of the smears with a negative reading.

Reactivation (relapse) – tuberculosis reactivation indicates recurrence of the disease after it has been considered cured. Bacteriologically confirmed reactivations belong to the influx of "new" sources of infection and should be reported separately among the "newly reported" cases.

Relapse: see "Reactivation".

RTC – Regional Tuberculosis Coordinator.

Sensitivity test – a culture procedure to determine whether growth of tubercle bacilli is inhibited by a certain drug. Bacilli which do not grow when incubated on a medium containing a given drug are said to be sensitive to that drug; bacilli that grow despite the presence of a given drug in the culture medium, are said to be resistant to that drug. Sensitivity tests should be carried out under standardized conditions in a Tuberculosis Reference Laboratory. They are relatively unimportant when new patients are started on treatment but are of considerable value in the treatment of relapses and failure cases.

Smear-positive index case – a new patient with smear-positive pulmonary tuberculosis. Smear-positive cases are highly infectious and, in particular, children belonging to the household of such an index case run a high risk of becoming infected with tuberculosis and to develop disease. Consequently, household contacts of smear-positive index cases are examined to identify secondary cases of tuberculosis.

Sputum conversion – the process whereby initially smear-positive patients become sputum AFB-negative while on adequate chemotherapy. In initially smear-positive patients who are treated with a standard (12-month) regimen, the change from AFB-positivity to AFB-negativity should, when patients are responding well, occur within 6 months after the start of treatment. A patient on standard chemotherapy who is still AFB-positive 6 months or more after the start of chemotherapy should be suspected of failure and retreatment ought to be considered. As a rule, patients who respond well on short-course chemotherapy will be negative within 3-4 months after the start of treatment.

Symptomatic suspect – a patient with symptoms suggestive of tuberculosis, who should, therefore, be suspected of suffering from the disease and who requires further investigation. The most important symptoms which should lead to suspecting tuberculosis are cough, which is usually productive and has been persisting for 3 weeks or more, haemoptysis and weight loss. All suspects aged 8 years and over should have their sputum examined for AFB.

Toxicity – serious disturbances in the human metabolism caused by a certain drug, which may cause irreversible damage or endanger the patient's life, which require immediate medical intervention (for mild disturbances see under drug intolerance). Examples of toxicity: deafness due to streptomycin, hepatitis due to isoniazid or rifampicin, exfoliative dermatitis due to thiacetazone.

Triple drug therapy – daily treatment with 3 drugs. Most modern treatment regimens for tuberculosis consist of 2 phases: an initial intensive phase of several weeks during which 3 (triple drug therapy) or 4 drugs are given with, *inter alia*, the aim of quickly reducing the number of viable bacilli, and a continuation phase of several months with, usually, the administration of 2 drugs.

Tuberculosis infection rate – see "Annual average risk of tuberculous infection".

Tuberculin survey – a study in which a representative group of individuals is tested with tuberculin with the aim of measuring the prevalence (see above) of infection with *M. tuberculosis* or *M. bovis*. To perform the tuberculin test, an intradermal

injection of 0.1 ml tuberculin (Purified Protein Derivative = PPD) is given in the forearm. Three days later, the reaction (an induration at the injection site), if present, is measured. A person is considered to have been infected in the past when the diameter of the induration measures 10 mm or more. Non-BCG-vaccinated children, usually of school age, are studied in a tuberculin survey. Based on the prevalence of infection the risk of infection with *M. tuberculosis* can thus be estimated. (See also "Average annual risk of tuberculous infection".)

APPENDICES

APPENDIX A

RATIONALE, AIM AND STRUCTURE OF A NATIONAL TUBERCULOSIS PROGRAMME

1. RATIONALE FOR A NATIONAL TUBERCULOSIS PROGRAMME

Tuberculosis is one of the few major killing infectious diseases steadily decreasing in developed countries, but uncontrolled in many developing countries. It should be controlled and eventually eliminated in the whole world for the following reasons:

1.1 Unlike many other infectious diseases seen in developing countries, tuberculosis can be controlled with the tools available nowadays, under any socio-economic conditions because *the infectious agent is nearly exclusively in the diseased man* who can quickly be rendered non-infectious.

1.2 We know now that it is not prevention of tuberculosis by mass BCG vaccination, but *case-finding of infectious cases of tuberculosis and their cure* which are the key to effective control of the disease, both in developed and developing countries. In addition, case-finding and treatment reduce suffering and, if adequately applied, prevent death from tuberculosis.

1.3 Since a balance also exists in developing countries between the tubercle bacillus and man (as it did in developed countries), in the absence of man-made interference (case-finding and chemotherapy), any reduction of sources of infection will inevitably improve the epidemiological situation. If *all* (or nearly all) *smear-positive cases of pulmonary tuberculosis currently diagnosed* in any developing country could be *rendered non-infectious*, the annual risk of tuberculous infection would immediately start to decrease.

1.4 Reliable *diagnostic tools* which allow detection of the great majority of cases of bacillary pulmonary tuberculosis, and *highly efficient chemotherapy regimens* which enable cure of nearly all discovered cases of tuberculosis are available.

2. AIM OF A NATIONAL TUBERCULOSIS PROGRAMME

The aim of a National Tuberculosis Programme (NTP) is two-fold :

- firstly, to diagnose and cure as many tuberculous patients as possible, and
- secondly, to reduce the *incidence* of the disease, so that tuberculosis ceases to be a public health problem.

To achieve this aim the NTP must be :

2.1 Country-wide with a rural focus, because the great majority of the population in developing countries lives in rural areas.

2.2 Permanent, as the tuberculosis problem has a firm grip over the population in most developing countries. The situation can be improved gradually, provided the NTP is implemented efficiently for at least a generation.

2.3 Adapted to the requirements of the population. In particular, it should be as convenient as possible for those receiving health care, whilst maintaining high operational efficiency for health workers.

2.4 The only way to meet the requirements under 2.1 to 2.3 in developing countries is to *integrate* the NTP into the existing health structure. No attempt should be made to set up an independent specialized service. Case-finding and treatment can be carried out at the general health facilities, and can be performed by paramedical workers, if they are properly trained and regularly supervised.

3. STRUCTURE OF A NATIONAL TUBERCULOSIS PROGRAMME

Though the NTP falls within the general health service framework, it needs in all developing countries, at the present stage, a managerial and supervisory staff dealing solely with tuberculosis. In most developing countries this staff is found at two levels in the NTP:

3.1 At the *Ministry of Health* where a Central Tuberculosis Unit is responsible for tuberculosis control in the whole country. The main Central Tuberculosis Unit's functions are as follows:

3.1.1 Planning of the operational steps in implementing, monitoring and evaluating the NTP.

3.1.2 Coordination of the NTP
- at intermediate and peripheral levels, and
- with other sections of the Ministry of Health.

3.1.3 Acquisition and distribution of supplies needed for the NTP, especially:
- drugs, in collaboration with the Central Medical Store (to check whether drugs are ordered, delivered, stored and distributed to the intermediate and the peripheral levels);
- laboratory equipment and stains, in collaboration with the laboratory services of the Ministry of Health;
- documentation.

3.1.4. Training of the personnel involved in the NTP.

3.2 In the *provinces* (regions): The Provincial (Regional) Director of Health is responsible for carrying out the NTP in the province (region). The Provincial (Regional) Director of Health, in consultation with the Central Tuberculosis Unit, appoints an officer known as the Provincial (Regional) Tuberculosis Coordinator (PTC or RTC), a Medical Officer, a Medical Assistant or a nurse.

The functions of the PTC (RTC) are :

3.2.1. To work closely with the Central Tuberculosis Unit in the performance of his duties as outlined under 3.1.1 to 3.1.3.

3.2.2 To coordinate tuberculosis control in the districts and to supervise the personnel involved in case-finding and treatment of tuberculosis. The PTC (RTC) is expected to visit each district at least once every six months.

Districts with a poor performance should receive special attention. The PTC (RTC) will discuss deficiencies in treatment and case-finding observed during his visit to the respective district with the District Chief Medical Officer (DCMO) and propose improvements.

3.2.3 To organize training programmes in the region in collaboration with the Central Tuberculosis Unit and the DCMO and to give on-the-job training to district and peripheral workers.

3.2.4 To ensure that the requested reports on case-finding and on results of chemotherapy are made in each district and sent to him. The PTC (RTC) checks and comments on the reports received from the districts and produces a report covering the whole province (region) for the attention of the Central Tuberculosis Unit.

3.2.5 The PTC (RTC) ensures close cooperation between the staff involved in case-finding and treatment of tuberculosis, and the microscopy service.

3.3 In the *districts:* The DCMO is responsible for carrying out the NTP in his district. As a rule, there is no district managerial and supervisory staff dealing solely with tuberculosis.

Responsibilities and tasks of the DCMO are:

3.3.1 To implement the NTP through the staff of district health workers.

3.3.2 To supervise treatment throughout the district and particularly ensure that:

- NTP regimens are prescribed;
- patients under treatment are closely supervised by the health workers;
- regimens are given for the required period, and that cured patients are discharged from treatment;
- sputum is examined for tubercle bacilli at the requested intervals;
- patients are referred to the DCMO or PTC (RTC) for possible retreatment following failure of chemotherapy for any given reason.

3.3.3 To assist health workers in the extension of tuberculosis case-finding in all existing health facilities in the district.

3.3.4 To visit the microscopy centres in the district regularly and check whether all newly diagnosed smear-positive cases are under adequate treatment.

3.3.5 To supervise updating and accuracy of Tuberculosis Registers and check that the documentation on case-finding and treatment is properly filled in.

3.3.6 To be responsible for procuring supplies, namely drugs, laboratory reagents,

sputum containers and forms for the district, and for distributing them to the health units in the district.

3.4 At the level of *health centres* and *health posts:* All health units should be involved in tuberculosis activities. In addition to other day-to-day medical work, the staff of the units is responsible for case-finding and treatment, including tracing of irregular attenders. The staff is also responsible for obtaining drugs and other supplies, keeping accurate records and giving health education to patients and the community.

APPENDIX B

EXTENT OF THE TUBERCULOSIS PROBLEM AND ITS TREND IN DEVELOPING COUNTRIES

In order to plan an efficient NTP, it is necessary to have a reasonable idea of the extent of the tuberculosis problem in the country. It is evident that this notion is impossible to obtain directly in most developing countries because of the lack of basic epidemiological data, even on a limited scale.

Two epidemiological indices are currently considered the most relevant to measure the epidemiological situation of tuberculosis and its trend in a given community.

1. INCIDENCE OF TUBERCULOUS PATIENTS EXCRETING TUBERCLE BACILLI DEMONSTRABLE BY DIRECT SMEAR EXAMINATION

This epidemiological index cannot be used in most developing countries since case-finding of smear-positive tuberculosis is very deficient in the majority of them. There is evidence that in many developing countries as few as approximately one third of smear-positive cases –the transmitters of the disease– are diagnosed. The incidence of tuberculous patients positive by direct smear is closely related to the quality and extent of case-finding methods.

Note : Although a well-conducted prevalence survey gives reliable information on the magnitude of the pool of infectious sources in the community, this does *not* imply that the prevalence survey is a reliable epidemiological index of the *epidemiological situation of tuberculosis and its trend.* It can be influenced either way by the extent of case-finding and quality of chemotherapy. Moreover, it is very expensive and needs a highly qualified staff.

2. THE RISK OF TUBERCULOUS INFECTION

There is general agreement that the annual risk of tuberculous infection is at present the best single indicator for evaluation of the tuberculosis epidemiological situation and its trend, both in developed and developing countries.

Unlike mortality and notification rates, it is not directly related to the procedures of the tuberculosis programme.

The annual tuberculosis infection rate can be derived from tuberculin test results in non-BCG-vaccinated schoolchildren. It was found that a 1 % annual risk of tuberculous infection corresponds to an incidence of about 50 smear-positive cases of pulmonary tuberculosis per 100,000 general population.

Note : It is not easy to conduct a reliable tuberculin survey, since it must be representative for the country or the area under study, and it must be carried out by a trained staff using standard procedures for testing and reading. Assistance can be asked from Dr. M.A. Bleiker, International Tuberculosis Surveillance Centre, P.O. Box 146, The Hague, Netherlands.

For evaluation of the *trend* of the tuberculosis epidemiological situation, at least 2 tuberculin surveys in a representative sample of non-BCG-vaccinated children or young adults of the same age or age-group tested by the same technique should be carried out at intervals of, say, 5 years.

APPENDIX C

TECHNICAL POLICIES FOR CASE-FINDING AND DIAGNOSIS

1. PRACTICAL METHODS

The following methods of case-finding are simple and lead to the discovery of most smear-positive cases of pulmonary tuberculosis:

- the examination of patients who present themselves with relevant symptoms to any health facility;
- the education of the community, the doctors and *all* the health staff on the importance of respiratory symptoms, especially persistent and productive cough, blood-stained sputum and chest pain, particularly if they persist for more than 3 weeks;
- the examination of contacts, in particular of smear-positive patients, with relevant symptoms;
- the bacteriological examination of patients who for any reason have had a chest X-ray showing a possibly tuberculous lesion.

2. WHERE TO ORGANIZE CASE-FINDING

The DCMO (DTC) will organize case-finding in the following health facilities and institutions:

- general and other hospitals,
- health centres,
- health posts,
- health village posts,
- prisons.

3. COLLECTION OF SPUTUM SPECIMENS FROM SUSPECTS

Wherever tuberculosis is suspected, three sputum specimens should be collected and sent for direct microscopy. Whenever possible, they should be taken within two days.

While waiting for laboratory reports on smear examinations, a course of symptomatic treatment may be given, if necessary including antibiotics, provided these are *not* those used for tuberculosis (e.g. *not* streptomycin *nor* rifampicin).

4. TECHNIQUE FOR COLLECTING SPUTUM

General rules:

- A specimen collected under the supervision of a competent person (Medical Assistant, nurse, health agent) is likely to be better than a specimen collected without supervision.
- Whenever possible, sputum collection should take place *in the open air.* (If not, it should be collected in a well-ventilated room, used only for this purpose.)
- Patients usually cooperate better if they are out of sight of other patients at the time of collection.
- Patients who have been chewing food immediately before sputum collection should rinse their mouths with water first.

Before collecting any sputum specimen:

- Briefly explain to the patient the reasons for sputum collection.
- Fill in the "Request Form for Sputum Examination".
- Write on the side and on the lid of a sputum container the same number as is written on the form.

How to collect a sputum specimen:

- Ask the patient to cough deeply. (Demonstration is usually more effective than words.)
- Ensure that no one is standing in front of a patient producing sputum.
- Avoid contaminating with sputum the outside of the sputum container. If the outside is contaminated, discard the container and repeat the collection with a fresh container.
- If the specimen is not suitable (e.g. if it is insufficient, or if it is only saliva), ask the patient to repeat the coughing until sufficient of the best possible sputum has been obtained (about 3-5 ml).

After collecting a sputum specimen:

- Place the lid on the container and close it firmly.
- Wash your hands with soap and water.
- Store sputum specimens preferably in a refrigerator or else in a cool, safe and dark place, such as a cupboard that can be locked and which is used solely for this purpose.
- Send specimens to the laboratory as soon as possible, but not later than one week after the sputum was collected.
- Accompany each specimen by a duly filled-in "Request Form for Sputum Examination".

N.B. 1: If an overnight specimen is needed, give the patient a container and ask him to bring sputum next day. Impress on the patient the necessity of spitting into this container as soon as he coughs up sputum in the morning. Make sure that the patient knows how to close the container and that he must bring it to the health unit as soon as possible.

N.B. 2: Special attention should be paid to any patient who gives a *history of tuberculosis or antituberculosis therapy.* Sputum specimen should be taken on 3 successive days and if any specimen is positive the patient should be seen by a Medical Officer who should try to get a detailed history of the previous treatment. Only in this way can a decision on adequate treatment be taken quickly.

N.B. 3: Children with persistent cough, who are often not able to produce sputum, must be sent to a hospital for examination.

5. TRANSPORT OF SPUTUM SPECIMENS

Lack of transport can be a major obstacle in case-finding, particularly in remote areas.

Any sputum specimen collected more than one week before it can be examined by microscopy is of limited use. Sputum specimens in containers must be suitably packed and sent by any means available to the microscopy centre together with the "Request Form for Sputum Examination". Every staff member in every health unit is responsible for seeing that specimens are sent to the laboratory as soon as possible.

Transport is a difficult problem, but experience has shown that if all means of transport in the area are used, sputum specimens can reach the microscopy centre within a reasonable time. Similarly, it should always be possible for the results of the laboratory examinations to be reported back to the peripheral health unit in a short time.

6. WHO COLLECTS SPUTUM SPECIMENS AND CONTACTS THE LABORATORY?

Health workers identify patients with symptoms of pulmonary tuberculosis, collect sputum specimens and contact the laboratory. These health workers also identify contacts of smear-positive patients. Among all out-patients attending any health institution, patients with respiratory symptoms of 3 weeks' duration or more should be selected for sputum examination.

APPENDIX D

FORMS *

1. GENERAL REMARKS

The accurate keeping of records on all individual patients, and periodical reporting –with statistics on patients and activities, together with explanatory remarks– is essential to the management of the NTP.

The numbers and designs of the documents in the NTP have been limited and simplified. A careful appraisal will show that it is not possible to reduce the clerical workload further, if we are to maintain both good patient care and the regular assessment of the programme.

The forms are designed and distributed to the periphery by the NTP authorities.

2. RECORDING AND REPORTING MATERIALS

The following records are to be kept:

2.1 *Tuberculosis Laboratory Register:* kept at laboratories carrying out sputum examination for tubercle bacilli (Form 1).

For each smear examined the information required must be entered by the microscopist or technician who carries out the smear examination.

The register contains, among others:

- serial number of sputum smear,
- date of examination,
- name and address of patient,
- examination for diagnosis or for follow-up of treatment,
- result of examination.

The Register gives information on the number of suspects examined, the number of smear-positive cases detected, and the number and results of smear examination for follow-up of treatment.

The person in charge of the Tuberculosis Register must check regularly whether all patients with positive smears in the Tuberculosis Laboratory Register are entered in the Tuberculosis Register.

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* See Forms 1-6 reproduced at the end of the book.

2.2 *Tuberculosis Register:* kept at district or health centre level (Form 2).

The Register contains, among others:

- type of tuberculosis (*P*ulmonary, *E*xtra-*P*ulmonary);
- classification of the case (New, Relapse, Transferred in from elsewhere, Treatment after return from defaulting, Others);
- dates and results of sputum smear and culture examinations:
  by direct smear at 0, 5, 8 and 12 (or more) months for patients treated with standard regimen; by direct smear at 0, 2, 5 and 8 months and by culture examination at 0, 2 and 8 months for patients treated with short-course chemotherapy;
- results of treatment:
  - cured (bacteriological examination negative),
  - treatment completed (no bacteriology results),
  - died,
  - positive at the end of treatment (continuing treatment),
  - out of control (defaulter),
  - transferred out to another district.

2.3 *Tuberculosis Treatment Card:* kept at every health unit giving treatment (Form 3).

It is kept for each patient under treatment within the framework of the NTP. It includes, among others:

- recording on injections of streptomycin (Note: immediately after the injection has been given, this should be entered on the Tuberculosis Treatment Card);
- dates of drug collection;
- clinical notes, etc.

2.4 *Patient's Identity Card:* kept by the patient.

It should contain:

- name, age, sex and address of the patient,
- health unit identification No.,
- Tuberculosis Register No.,
- name of the health unit,
- type of tuberculosis,
- start of treatment (date),
- regimen used,
- space for dates of appointments.

2.5 *Request Form for Sputum Examination:* kept at all health units (Form 4).

It contains:

- name of treatment unit, date of the request,

- patient's name, age, sex, address,
- type of tuberculosis (pulmonary, extra-pulmonary),
- new patient/follow-up of chemotherapy,
- specimen identification No., patient's Tuberculosis Register No.,
- date of sputum collection,
- results of sputum examination (to be completed in Laboratory).

2.6 *Request Form for Culture and Sensitivity Tests of M. tuberculosis:* kept in hospitals. It is usually designed by the Central tuberculosis Unit.

2.7 *Quarterly Report on New Cases and Relapses:* kept at district or health centre level (Form 5).

2.8 *Quarterly Report on Results of Treatment of Smear-positive Cases of Pulmonary Tuberculosis registered 15-18 months earlier:* kept at district or health centre level (Form 6).

The health worker keeping a Tuberculosis Register has to report, for his area (district or health centre), all new smear-positive and smear-negative pulmonary cases, smear-positive pulmonary relapses and new extra-pulmonary cases to the PTC (RTC) for each quarter of the year.

How to make the report?

The Tuberculosis Register is used to prepare this report. It is obvious that reliable reports can only be produced if the Tuberculosis Register is kept up-to-date.

To prepare the report, go through the last page(s) of the Tuberculosis Register and identify patients who were registered during the quarter concerned. Count now, looking at the columns "Classification" and "Smear result at 0 month", the number of new male smear-positive cases; enter the total on the report form. Continue with the new female smear-positive cases, then male smear-negative pulmonary cases, etc. Put a mark after each patient who has been reported on and check at the end if all patients have been included in the report. Mark separately and distinctly the last patient in the Tuberculosis Register for the quarter concerned (leave space after each quarter in the Tuberculosis Register).

Note 1: relapses reported in block 1 should include only smear-positive relapses;

Note 2: the report should include only *new* cases and smear-positive relapses. Cases who were transferred in or who returned to control, should *not* be included.

The Quarterly Report should reach the PTC (RTC) before:

1st Quarter – April 30, same year
2nd Quarter – July 31, same year
3rd Quarter – October 31, same year
4th Quarter – January 31, following year.

The PTC (RTC) will produce a Quarterly Report covering the whole province (region) by district, and send it as soon as possible to the National Supervisor of the NTP.

Identify first in the Tuberculosis Register smear-positive pulmonary tuberculosis patients registered during the quarter concerned (this is easy when the beginning and the end of the quarter were clearly marked during the preparation of the Quarterly Report on Case-finding). Note that the number of patients identified should equal the number of new smear-positive cases which were reported in the Quarterly Report on New Cases and Relapses for the quarter concerned. Each identified patient should be counted twice on the Report Form: first in column 0 ("patients registered...") and secondly in one of the columns 1 to 6, indicating the result of treatment.

Note that:

- a patient can only be reported "cured: smear-negative" when at least two negative smear results have been obtained with an interval of three months or more;
- patients may be "continuing treatment" because of treatment failure. Such cases should be given the retreatment regimen (see Appendix E.III.). It should not happen that cases are still on treatment 15 months or more after the start of chemotherapy because of irregularity or of negligence in discharging the patient.

Count at the end the number of patients entered in each column. The sum of the columns 1-6 should equal the total of column 0.

Information on patients registered, for example, in 1984 should be reported as follows:

Period of registration	*Assessment date*	*Last reporting date*
1st Quarter 1984	June 30, 1985	July 31, 1985
2nd Quarter 1984	September 30, 1985	October 31, 1985
3rd Quarter 1984	December 31, 1985	January 31, 1986
4th Quarter 1984	March 31, 1986	April 30, 1986

Taking patients registered in 1984 as an example, the health worker responsible for NTP in the district will produce a Quarterly Report covering the whole district before August 31, 1985; November 30, 1985; February 28, 1986; and May 31, 1986.

The PTC (RTC) will produce a Quarterly Report covering the whole province (region) by district, and send it as soon as possible to the National Supervisor of the NTP.

2.9 *Referral and Transfer Form*

A form should be filled in for:

- every patient who is referred to another unit (refer),
- every patient who is moving to another village and will continue treatment at another unit (transfer).

Part A of the form should be filled in by the referring unit:

- from health post/health centre/hospital ..... (name of the referring/transferring unit),
- to health post/health centre/hospital ..... (name of the unit the patient is referred/transferred to),
- name, age and sex of the patient,
- address of the patient,
- number of Tuberculosis Register,
- type of tuberculosis,
- date the patient started treatment,
- results of sputum examination,
- regimen prescribed at the referring unit,
- treatment to be given at the receiving unit,
- category under which the patient should be registered at the receiving unit (new, retreatment, transfer-in, others),
- name, designation and signature of person who filled in the form.

After part A has been filled in in duplicate, one copy of the form should be given to the patient, who takes it to the unit to which he has been referred/transferred, while a second copy is sent by mail or brought to that unit.

Part B should be completed by the unit to which the patient was sent and should be returned immediately after the patient presents himself for treatment at the new unit:

- from health post/health centre/hospital ..... (name of the unit the patient was referred/transferred to),
- to health post/health centre/hospital ..... (name of the unit which referred/transferred the patient),
- name, age and sex of the patient,
- number of Tuberculosis Register at former unit,
- date the patient arrived at the unit to which he was referred/transferred,
- name, designation and signature of person who filled in part B of the form.

APPENDIX E

CHEMOTHERAPY

I. STANDARD REGIMENS FOR NEWLY DIAGNOSED CASES OF TUBERCULOSIS

1. The two main *standard regimens* recommended for use in programme conditions in developing countries are:

1.1 Isoniazid plus thiacetazone (in a combined tablet) daily for 12 months, supplemented, whenever possible, by streptomycin daily for the first 2 months of chemotherapy.

1.2 A twice-weekly, fully supervised regimen of streptomycin plus isoniazid, preceded, whenever possible, by an initial intensive daily phase of the two drugs.

2. Drug dosages

2.1 *Streptomycin* is given by intramuscular injection once daily for 2 months. The dose is 1 g daily for adults weighing more than 50 kg or below the age of 45 years. For those weighing less than 50 kg or over 45 years old the daily dose is 0.75 g. Streptomycin may be omitted on Sundays in out-patients.

The dose in children: for those weighing up to 10 kg – 0.25 g; for those weighing 11 to 20 kg – 0.50 g; and for those weighing 21 kg or more – 0.75 g.

N.B. 1. If streptomycin cannot be given because of severe side-effects, substitute it with ethambutol at a dose of 25 mg/kg body weight by mouth daily for 2 months. Streptomycin should only be used for the treatment of tuberculosis, not for other diseases.

2.2 In developing countries, *isoniazid and thiacetazone* (a combined tablet) are the most important drugs in the treatment of newly diagnosed cases of tuberculosis with no previous chemotherapy, if thiacetazone is reasonably tolerated. One tablet contains either 300 mg isoniazid and 150 mg thiacetazone, or 100 mg isoniazid and 50 mg thiacetazone. The daily dose for adults is 1 tablet of 300 mg isoniazid and 150 mg thiacetazone.

The daily dose for children is shown in Table 1.

Table 1

Daily dose of Thiazina (isoniazid 100 mg and thiacetazone 50 mg) for children

Weight of patients (at start of chemotherapy)	Number of combined tablets (isoniazid *100 mg* and thiacetazone *50 mg*)
Up to 10 kg	1/2
11 to 20 kg	1
21 to 30 kg	2
30 kg and over	3

2.3 *Isoniazid in the continuation phase of the regimen under 1.2* above (isoniazid and streptomycin twice weekly): 15 mg of INH per kg body weight (in adults this corresponds to a total of 450 mg to 700 mg on the days it is taken).

N.B. 2. If the standard regimen under 1.1 (isoniazid plus thiacetazone supplemented by streptomycin in the initial intensive phase) cannot be applied because of side-effects of thiacetazone, and the regimen under 1.2 (streptomycin plus isoniazid) cannot be given because the patient cannot come regularly twice a week to the nearest health unit, another "standard" regimen is recommended:

Isoniazid plus ethambutol supplemented by streptomycin daily during the first 2 months (as out-patient or in-patient in hospital or hostel), followed by isoniazid and ethambutol daily or twice weekly (at higher doses) for a further 10 months (as out-patient).

Ethambutol at the daily dose of 15 mg and twice-weekly dose of 30 mg per kg body weight has largely replaced thiacetazone and PAS by now, because it is better tolerated but, unfortunately, it is rather expensive.

Ethambutol at the dose of 25 mg daily in the first 2 months is definitely better; but in the developing countries, it is not commendable to have different tablets of ethambutol. After 2 months' treatment with ethambutol 25 mg, there will be a very high risk of side-effects if the health workers forget to give 15 mg tablets for the remainder of the treatment period.

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II. SHORT-COURSE CHEMOTHERAPY FOR NEWLY DIAGNOSED CASES OF TUBERCULOSIS

Short-course chemotherapy should only be given, as a rule, to patients with newly diagnosed pulmonary tuberculosis whose sputum is *positive by microscopy*. This chemotherapy should also be prescribed to smear-negative patients with miliary tuberculosis, tuberculous meningitis or another very serious form of smear-negative tuberculosis.

The full *regimen* is:
isoniazid + rifampicin + pyrazinamide + streptomycin daily for 8 weeks, followed by Thiazina (isoniazid + thiacetazone) daily for a further 24 weeks.

Regimen and dosages are summarized in Table 2.

Table 2

Regimen and dosages of drugs for adults

	DAILY DURING WEEKS 1-8°			DAILY DURING WEEKS 9-32
	S	HR	Z	TH
Pre-treatment weight	streptomycin intramuscular injection	isoniazid 100 mg rifampicin 150 mg (combined tablets)	pyrazinamide 0.5 g tablets	isoniazid 300 mg thiacetaz. 150 mg (combined tablets)
51 kg and more	1 g*	4	4	1 (3)**
33 kg – 50 kg	0.75 g	3	3	1 (3)**
less than 33 kg	0.75 g	2	2	(2)** tablets 100/50 mg

° If the direct smear is positive at the end of the 8-week initial intensive phase, the daily SHRZ regimen will be continued, as a rule, for another 2 to 4 weeks.

* Patients aged more than 45 years should receive 0.75 g; streptomycin should not be given during pregnancy.

** In brackets: number of combined tablets of isoniazid 100 mg and thiacetazone 50 mg.

The dosage of all the drugs is related to the patient's weight at the start of treatment (pre-treatment weight). Reduced dosages of rifampicin and pyrazinamide are given to patients who weigh less than 50 kg. Reduced dosages of streptomycin are given to patients weighing less than 50 kg or aged over 45 years.

N.B. Doses in children:
streptomycin – 20 mg per kg body weight (but no more than 1 g); rifampicin – 10 mg per kg body weight (but no more than 600 mg); pyrazinamide – 30 mg per kg body weight (but no more than 2 g).
(Isoniazid is usually in a combined tablet with rifampicin.)

In the continuation phase, children will receive the following doses of Thiazina: those weighing under 10 kg – 1/2 tablet of isoniazid *100* mg, thiacetazone *50* mg; those weighing 11-20 kg – 1 tablet of isoniazid *100* mg and thiacetazone *50* mg; those weighing 21-30 kg – 1 1/2 combined tablets of isoniazid *100* mg and thiacetazone *50* mg; for those weighing more than 30 kg see Table 2.

Patients from rural areas will have, as a rule, the initial intensive phase of chemotherapy as in-patients, since every dose of drugs should be given under strict staff supervision:

a) the oral drugs should be given on an empty stomach in a single dose immediately before the streptomycin injection;

b) the oral drugs must be swallowed under direct supervision of a member of staff;

c) rifampicin should never be handed out to the patient.

Rifampicin, as streptomycin, should be used only for the treatment of tuberculosis.

In urban areas, patients can receive the initial intensive phase of short-course chemotherapy on an ambulatory basis provided that they can attend daily (except on Sundays) for supervised treatment at the treating centre. The patient will then attend the health unit daily (except on Sundays) and will receive his treatment under strict supervision; rifampicin should not be given to the patient to take home (thereby preventing abuse of the drug). Sputum of the patient will be examined by microscopy 2 months after the start of chemotherapy:

1. If results of smear examinations after 2 months are negative, the initial intensive phase will be discontinued.
2. If the result of the smear examination after 2 months is positive, the intensive chemotherapy will be continued, as a rule, for another 2 to 4 weeks.

After completion of the initial phase, the patient should be started on Thiazina, a few days before he is discharged from the hospital. It is likely that this will improve compliance after discharge from hospital. At the time of discharge the patient will take with him sufficient Thiazina tablets for a period of 4 weeks; he should be properly instructed about the use of the drugs. A patient who absconded, i.e. who left hospital before having completed the 2 months of initial intensive chemotherapy, will continue with Thiazina until he has been treated for a total period of 12 months.

In case the direct smear is still positive 5 months (20 weeks) after the start of treatment, the patient should be admitted for retreatment.

In all cases treated with Thiazina during the continuation phase, sputum will be examined by microscopy for *acid-fast bacilli,* 5 and 8 months after the start of chemotherapy. The patient will be discharged from treatment if:

- he has completed 6 months of Thiazina, and
- the direct smears at 5 and 8 months are negative for acid-fast bacilli.

A patient who is irregular in his collection of Thiazina will continue with Thiazina until he has completed 6 months.

In case the direct smears at 5 and/or 8 months are positive, the patient should be admitted for retreatment.

III. RETREATMENT OF SMEAR-POSITIVE RELAPSES AND FAILURE CASES

The retreatment regimen consists of an initial intensive phase of 5 drugs, given daily for a total period of at least 3 months (12 weeks) [except for streptomycin which is given for 2 months (8 weeks) only], and a continuation phase of 5 months, of which the prescribed drugs depend on the results of the sensitivity test to isoniazid (if this is available):

initial intensive phase: rifampicin (combined with isoniazid), pyrazinamide and ethambutol daily for at least 3 months (12 weeks), supplemented with streptomycin for the first 2 months (8 weeks); the intensive phase will be continued until:

1. results of sensitivity tests have been received, *and*
2. at least the last result of the (monthly) sputum examination by direct smear is negative (at 2 and/or 3 months after the start of chemotherapy).

continuation phase:

1. patients harbouring strains which are fully or partially resistant to isoniazid will continue with rifampicin (combined with isoniazid) and ethambutol three times weekly for a further 5 months under supervision (5 RHE3).
2. patients harbouring strains *fully* sensitive to isoniazid will continue with isoniazid and thiacetazone – combined tablets (Thiazina) – daily for 5 months.

If no culture facilities are available, the patient will continue with 5 RHE3. The regimen and dosages for adults are summarized in Table 3.

Table 3

Regimen and dosages of drugs for adults

	Initial phase				Continuation phase		
					H-resistant		H-sensitive
	Daily during months 1-3 (a)				Three times weekly during months 4-8		Daily during months 4-8
	RH	Z	E*	S (b)	RH	E*	TH
Pre-treatment weight	R 150 mg H 100 mg (combined tablets)	Z 0.5 g tablets	E 0.4 g tablets		R 150 mg H 100 mg (combined tablets)	E 0.4 g tablets	H 300 mg thiacet. 150 mg (combined tablets)
51 kg or more	4	4	3-4	0.75 g	4	4-5	1 (3)**
33 kg – 50 kg	3	3	2-3	0.75 g	3	3-4	1 (3)**
less than 33 kg	2	2	2	0.50 g	2	2-3	– (2)**

* The dose of ethambutol is 15 mg per kg body weight when given daily and 30 mg/kg body weight when given three times weekly (see p. 51 under N.B. 2).

** In brackets: number of combined tablets of isoniazid 100 mg and thiacetazone 50 mg.

R = rifampicin
H = isoniazid
Z = pyrazinamide
E = ethambutol
S = streptomycin
TH = Thiazina (isoniazid + thiacetazone)

(a) The initial intensive phase will essentially be given for 3 months (12 weeks); as soon as results of sensitivity tests have been received *and* sputum is negative by direct smear *and* the patient has completed the intensive initial phase of 3 months (12 weeks), the continuation phase will start. If sputum is smear-positive at 3 months (12 weeks), the initial intensive phase of 4 drugs daily will be continued for another 4 weeks. If the patient is smear-positive at 4 months (16 weeks), all drugs will be stopped for 2-3 days and a specimen, labelled "URGENT", will be sent to the Reference Laboratory for culture and sensitivity tests, if such a facility is available.

(b) Streptomycin will be given for the first 2 months (8 weeks). The dosage of all drugs is related to the patient's weight at the start of treatment (pre-treatment weight).

All patients will have the initial intensive phase, as a rule, as in-patients. During in-patient treatment, every dose of the drug must be given under strict supervision:

- the drugs should be given in a single dose on an empty stomach before the injection of streptomycin;
- the drugs must be swallowed under the direct supervision of a staff member.

A careful history should be taken before admission, to ascertain whether the patient is a relapse or a failure case as defined under 6.4.1 and 6.4.2.

The diagnosis on admission should be based on 2 positive results of direct smear examination. A sputum specimen will be sent to the Reference Laboratory for smear and culture examination and sensitivity tests, *before* treatment is started (if such a facility is available).

Chemotherapy can be started the first day after collection of the specimen for culture examination. The specimen should reach the Reference Laboratory within 7 days and should therefore be sent without delay after collection.

When the initial intensive 3-month (12 week) phase has been completed and sputum is negative by direct smear, the regimen for the continuation phase can be chosen immediately after receipt of the results of the sensitivity test (see above).

TUBERCULOSIS LABORATORY REGISTER

Year _____

Lab Serial No	Date	Names (2)	Sex M/F	Age	Name of Treatment Unit	Address (in new patients)	Sputum from		Results Specimen			Signature	Remarks
							New patients *	Follow up **	1	2	3		

FORM 1

* these are diagnosed new or relapsed cases

** these are patients on chemotherapy, enter District TB No

TUBERCULOSIS TREATMENT CARD

NATIONAL TUBERCULOSIS PROGRAMME

District TB No. _____

Health Unit : _____

Name : _____

Address (in full) : _____

Sex : M ☐ F ☐ Age : ____ BCG : no scar ☐ scar seen ☐ scar dubious ☐

Type of patient

Pulmonary ☐ Extra-pulmonary ☐

New ☐ Relapse ☐

Transfer in ☐ Other (specify) ☐

Treatment after default ☐

I. INITIAL INTENSIVE PHASE

Prescribed regimen and dosages * :

New case ☐ (standard)

☐☐

S TH

New case ☐ (short-course)

☐☐☐

S RH Z

Retreatment ☐

☐☐☐☐

S RH Z E

(S for 2 months only)

S : streptomycin, TH : thiazina, RH : rifampicin and isoniazid

Z : pirazinamide, E : ethambutol

* Indicate daily number of tablets and dosage of S (grams)

Month	Results of sputum examination					WEIGHT (kg)
	Local lab		Reference lab *			
	Date	Smear	Smear	Cult	Sens	
0						
2						
5						
8						
≥ 12						

* for patients on short-course chemotherapy only

MONTH \ DAY*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

* Tick appropriate box after the drugs have been administered

Please turn over for continuation phase

FORM 3

II. CONTINUATION PHASE (see Guidelines)

Enter prescribed regimen and dosages
(indicate number of tablets per dose)

New case **standard** ☐ tablets TH daily (10 months)

New case **short-course** ☐ tablets TH daily (6 months)

Retreatment **INH-sensitive** ☐ tablets TH daily (5 months)

Retreatment **INH-resistant** ☐☐ 3 times weekly HR E (5 months)

MONTH / DAY*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

* Enter X on day of supervised drug administration or when drugs are collected (monthly TH collection for self administration)
Whenever drugs are collected for self supervised administration draw a horizontal line (———) to indicate number of days supply given

REMARKS _____

FORM 4

NATIONAL TUBERCULOSIS PROGRAMME
TB LABORATORY FORM
REQUEST FOR SPUTUM EXAMINATION

Name Treatment Unit _____ Date _____

Patient's Name _____ Age _____ SEX M F

Village/Street _____ T/A _____ District _____

Type of TB : Pulmonary ☐ Extra-Pulmonary ☐

New Patient *		Follow-up Examination **	

Specimen Identification No. _____ Patient's District Register No. _____

Date of Sputum Collection _____ Signature of Specimen Collector

* these are diagnosed new or relapsed cases
** these are patients on chemotherapy, enter District TB No.

RESULTS (To be completed in Laboratory)

Lab Serial No _____

(a) Appearance of sputum to the eye :

Muco-purulent ☐ /Blood-stained ☐ /Saliva ☐

(b) Microscopy :

Date	Specimen	Results *	Positive (grading)			
			+++	++	+	scanty
	1		☐	☐	☐	☐
	2		☐	☐	☐	☐
	3		☐	☐	☐	☐

* Write Neg or Pos

Date _____ Examined by (Signature) _____

The completed form with results should be sent to the treatment unit

NATIONAL TUBERCULOSIS PROGRAMME

FORM 5

Quarterly report on new cases and relapses of tuberculosis

Patients registered during

☐ quarter of 19

Name of District Tuberculosis

Coordinator: _____

Date of completion of this form : _____

Signature : _____

Name of district :

_____

Block 1

PULMONARY TUBERCULOSIS							EXTRA-PULMONARY TUBERCULOSIS (4)		TOTAL (5)		
SMEAR-POSITIVE					SMEAR-NEGATIVE (3)						
NEW CASES (1)			Relapses (2)								
Males	Females	Total	M	F	M	F	M	F	Males	Females	Total

SMEAR-POSITIVE NEW CASES from Column (1) above

Block 2

Age-group (years)														TOTAL		
0-14		15-24		25-34		35-44		45-54		55-64		65 or more				
M	F	M	F	M	F	M	F	M	F	M	F	M	F	Males	Females	Total

Explanations on how to fill in the form

Quarters : 1st quarter = January, February, March
2nd quarter = April, May, June
3rd quarter = July, August, September
4th quarter = October, November, December

Block 1 : NEW CASES AND RELAPSES OF TUBERCULOSIS registerer during quarter of (year)

Fill in the quarter and the year

Column (1) : SMEAR-POSITIVE NEW CASES = patients with pulmonary tuberculosis, sputum smear-positive, who have never received anti-tuberculosis treatment

Column (2) SMEAR POSITIVE Relapses = patients with pulmonary tuberculosis sputum smear-positive who have been declared cured but have now got the disease again

Column (3) SMEAR-NEGATIVE CASES = patients with pulmonary tuberculosis having a negative sputum for AFB, in whom the diagnosis of tuberculosis was made by means other than sputum microscopy

Column (4) : EXTRA-PULMONARY TUBERCULOSIS = patients with tuberculosis of organs other than the lungs

Column (5) : TOTAL Males — Add **all male** patients in columns 1 + 2 + 3 + 4
Females — Add **all female** patients in columns 1 + 2 + 3 + 4
Total — Add **all patients** (males + females) in columns 1 + 2 + 3 + 4

Block 2 : SMEAR-POSITIVE NEW CASES from Column (1) above

In this block enter the patients (already recorded in Block 1, column (1)) according to their sex and age group If the exact age of a patient, at the time of his registration, is unknown, it should be estimated to the nearest 5 years, e.g 15, 20, 25, etc

NATIONAL TUBERCULOSIS PROGRAMME

REPORT ON THE RESULTS OF TREATMENT OF SMEAR-POSITIVE PULMONARY TUBERCULOSIS PATIENTS REGISTERED 15-18 MONTHS EARLIER

Name of district : _____ Name of District Tuberculosis Coordinator : _____	Patients registered during ☐ quarter of 19	Date of completion of this form : _____ 19 _____ Signature :

Total No of smear-positive patients registered during the above quarter M	F	T*	Regimen	(1) Cured (smear-negative)	(2) Treatment completed (no smear-results)	(3) Died	(4) Failure (smear-positive)	(5) Defaulted	(6) Transferred to another district	Total number evaluated (sum of columns 1 to 6)
			1. **New Cases**							
			1.1 short-course							
			1.2 standard							
			1.3 Total							
			2. **Retreatment**							
			2.1 relapses							
			2.2 others (failure cases)							
			2.3 Total							

* Of those excluded _____ (number) from evaluation of chemotherapy for the following reasons : _____

_____

FORM 6

APS, Tours
Achevé d'imprimer sur les presses

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